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Transient epileptic amnesia: an under-diagnosed phenomenon? Three more cases

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Three cases of patients with transient epileptic amnesia (also known as pure amnestic seizure) are described. In two patients it was the unique seizure type and represented *de novo* epilepsy occurring in the elderly. In the third patient it coexisted with long standing complex partial seizure of mesial temporal lobe origin. The problems associated with the diagnosis and the main clinical features are discussed. In addition the underlining pathophysiological mechanisms are considered. It is argued that this seizure type is likely to be under-diagnosed and that further research is needed as the presence of TEA has significant implications for clinical and surgical management.

INTRODUCTION

Transient epileptic amnesia (TEA) is a term coined by Kapur[1] to characterize a singular seizure type in which the only ictal manifestation is a remarkable anterograde amnesia for all ictal facts and events, despite clear consciousness and purposeful behavioural responses and interaction with their surroundings, as documented by a witness. A similar phenomena was described by Palmini[2] and Gloor as pure amnestic seizure. According to these authors[1,2], 'patients were able, during such seizures, to engage in whatever activity appeared appropriate at that time', implying that, except for the inability to incorporate the ongoing activity and perceptions in long-term memory, their cognitive functioning during the seizure was intact, as judged by people around them. All cases described by Palmini *et al.* had clear-cut mesial temporal lobe epilepsy (MTLE) with its classical seizure semiology.

There are a few reports[3–9], however, indicating that seizures of this type are rarely the only ones presented by the patient, making the diagnosis, in this circumstance, extremely difficult.

The main differential diagnoses are transient global amnesia[10], somatization disorder with pseudoneurologic symptoms[11] (amnesia) and dissociative amnesia[12]. There are a many reports[2,13–16] in which ictal amnesia is the main clinical feature. A close inspection of the descriptions of the ictal behaviour reveal however, that these seizures showed some of the classical signs of MTLE, so that they should be classified as such. As indicated above, during TEA there are no signs of a seizure to an observer. The patient's behaviour is entirely appropriate, indeed, any abnormal behavioural change is an excluding criteria[2].

Over 30 patients have been reported that partially fulfill the diagnostic criteria of TEA. Of these, approximately one third have TEA as their unique seizure type[3–9]. Other reported clinical features of interest are: numerous episodes, onset generally in later life, episodes precipitated by sleep, coexistence of other seizure types, EEG abnormalities, favorable response to antiepileptic drugs, seizures with approximately 1 hour duration and cardiac risk factors[10]. Zeman *et al.*[17] have demonstrated, after a careful neuropsychological examination, that some of these patients also have a persistent interictal retrograde autobiographical memory impairment, in spite of the anterograde (ictal) deficits, implying interictal bilateral hippocampal disfunction.

The last two comprehensive reviews of published work on this subject were provided by Kapur[1] and recently by Zeman *et al.*[17]. However, as they have pointed out, no detailed neuroimaging studies of their patients were carried out[1,17].

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Here, three new cases are described, followed by a discussion of diagnosis and questions that could be posed for prospective studies.

Case 1

A 45-year-old man with a 20-year history of complex partial seizures, some with secondary generalization, was seen because of an increase in the number of his habitual seizures. He had been taking low inappropriate doses of three AEDs for years. Two of these drugs were slowly withdrawn and carbamazepine was increased up to 1400 mg/day. After 4 months he went on carbamazepine monotherapy. Two months later he was free of his habitual seizures but started noticing a new sort of 'blank spell'. He described that 15 days before, he had arrived home but with no idea of his journey. The following day he asked a colleague, who usually traveled with him, what had happened the day before. His colleague explained they had taken the usual bus and they had discussed a football match during their way home. His friend was interviewed afterwards. He remarked that the patient was completely normal during their conversation and he did not show any subtle signs of impaired consciousness. The patient was completely amnesic for the entire period. He was also unable to remember how he arrived home. Following a further increment in CBZ the 'blank spell' decreased in frequency although did not stop completely. He has been followed for 7 years without any significant change in the number of the 'blank spells' (TEA) but he is now free of secondary generalized seizures and has one or two partial complex seizures/year.

Case 2

A 71-year-old woman presented with a 6-month history of four episodes of 'completely forgetting'. One of these episodes was witnessed by the caretaker of her apartment building and the second indirectly by her son, during a phone call. In the first episode she went to a shop on a Saturday morning, as was her usual practice. When she arrived home the caretaker helped her carry her bags to her flat. Inside the lift she talked normally, without any sign of impaired consciousness or prolonged reaction time. In her flat while unpacking the bags, she suddenly asked the caretaker: 'Who has bought these? Who went to the supermarket? The caretaker replied: you did Miss, as you usually do on Saturday's mornings'. She repeatedly said: 'are you sure that I did'? 'I cannot remember leaving my house today! What is happening to me?'. The witness reported that, apart for her dazed appearance and repeated queries at the end of the episode, her behaviour was completely normal. She confirmed that she went to the shop by comparing the bill with the value in her checkbook. There was no clue of any alteration of her behaviour or awareness during the time he observed her. The second episode happened while she was phoning her son. They talked for approximately 40 min. She made arrangements for visiting him on the next weekend. Her son reported that she spoke normally, again without any delay in replying. During the call she did not show any sign of loosing track of the conversation. Two days later the son phoned to confirm her visit and noticed that she was amnesic for the whole event. She vigorously denied having phoned him and making arrangements for the visit. During the next 2 months she experienced two more episodes. One documented by a friend during a phone call, the last one was again witnessed by the caretaker. She was able to remember that she had forgotten what she had done before in episodes one, two and four and that she had repeatedly asked the caretaker. Her EEGs and brain MRI scan were normal; although no detailed assessment of the hippocampus was undertaken. The possible diagnosis was discussed, carbamazepine was introduced and tritated up to 600 mg daily. She has been followed for 3 years with no further episodes. No cognitive decline was observed, as assessed by a mini-mental state examination (MMSE), although she has always complained about memory impairment. She continued to live alone and independently when she was last seen.

Case 3

A 74-year-old man presented with a 2-month history of three episodes of 'forgetting and a little confusion' that lasted for almost 1 hour. Three of these episodes were witnessed by two different observers. Both were interviewed separately and confirmed that, besides his dazed appearance and repetitive questioning at the end of the episode, he appeared normal for the period that he was amnesic. In the first episode he and his wife had left their house to visit a friend. After almost 1 hour walking and talking normally, he suddenly asked her 'where are we now? Why did we come here?' He then became perplexed and asked the same question many times. He remembered having asked her these questions and that he did not know what they were going to do. The two other episodes were similar. A MRI scan was normal, although hippocampal volumes were not measured. He had two normal awake EEGs and only one demonstrated non-specific intermittent slowing (rare) over the fronto-temporal regions, without any side emphasis. The

possible diagnosis was discussed and he decided to take 250 mg of phenytoin. He has been followed for 3 years. After 1 year free of episodes, he decided to stop the phenytoin because he would like to drink alcohol during the Christmas period. Two weeks later he experienced a further episode, lasting almost 1 hour. He recommenced his AED again and thereafter he had no further episodes.

All patients have been followed prospectively; case 1 for 7 years and the two others for 3 years. Cases 2 and 3 have not developed any other type of seizures. All were seen four times a year during the follow up. In all appointments they had a MMSE with no evidence of cognitive decline over these years. Therefore, in two patients PAS was the sole manifestation of epilepsy. In cases 1 and 2 they were able to remember that they 'forgot' and this apparently characterized the end of the episodes. All patients were concerned about loosing their memory and had significant complaints about their memory for the last years of their lives.

Cases 2 and 3 had normal MRI scans, although there were no measurements of hippocampal volumes or relaxometry. Case 1 had only a normal CT scan.

DISCUSSION

All of the cases described fulfilled the diagnostic criteria proposed by Kapur[1], Palmini[2], Hodges[15] and Zeman[17]: (1) there was a history of recurrent witnessed episodes of transient amnesia; (2) cognitive functions other than memory were judged to be intact during typical episodes by a reliable witness; (3) there was other evidence for a diagnosis of epilepsy. This evidence was provided by either (a) an awake or sleeping EEG, or (b) the co-occurrence of other seizure types (if they had roughly concurrent onset and/or close association with episodes of transient amnesia this suggested a connection), or (c) a clear cut response to antiepileptic drugs (AEDs), or by a combination of these three factors.

There are many difficulties in making this diagnosis. Probably TEAs are under-diagnosed because neurologists, being unaware, do not specifically ask about their occurrence, nor are they reported by patients, who may not associate 'memory lapses' with their habitual seizures[18] or may blame AED or, in elderly patients, the aging process. I agree that there is no place for therapeutic tests[19] in making a diagnosis of epilepsy, however, it seems realistic to acknowledge that, in this specific situation, only with a favorable response to AED, after a long follow up, that a diagnosis of epilepsy is appropriate, mainly in those cases where EEGs and neuroimaging do not show any specific abnormality. This should be carried out after several events have been documented to be able to demonstrate a clear reduction in frequency, or a complete cessation after commencement of the AED.

I saw my first patient (case 1) before the publication of Kapur's[1] and Palmini's[2] paper. I must admit that prior to this, I had difficulties in interpreting these episodes. At that time my doubts were: (1) Was it a seizure? The episode neither lasted long enough (less than 1 hour) to be compatible with the diagnosis of TGA (usually more than 2 hours), nor was it short enough to be considered a complex partial seizure (usually less then 5 minutes); (2) If it was a seizure how could I explain the apparently normal behaviour during the seizures? I have only been able to make the diagnosis retrospectively.

Over 30 cases have been reported[1–9, 13–16]. This is likely to be a significant underestimation. It is very difficult to diagnose TEA. The diagnosis can only be made retrospectively or by being aware of its existence by inquiring specifically for such episodes in prospective studies.

At this time we a facing a diagnostic dilemma. Temporal features of TEA are neither long enough to fulfill the semiotic characteristics of transient global amnesia (usually more than 2 hours) nor short enough (almost 1 hour) for a complex partial seizure (usually less than 4 minutes).

I believe that clinicians need a high index of suspicion. Neurologists should include a detailed interview with the patient and when possible a witness, leading to accurate description of the circumstances and phenomenology of the TEA. As TEAs often coexist with complex partial seizures of temporal lobe origin[1, 2, 14, 15] neurologists must ask patients and caretakers directly for this specific manifestation of a seizure.

At some point, someone may ask why we should pay attention to such a rare sort of seizure? There are at least three reasons: (1) it is important to correctly diagnose it because there is an effective treatment; (2) it is likely, by the problems already discussed, that they might be not so rare; (3) patients are always distressed by them, fearing the onset of dementia.

PATHOPHYSIOLOGY

There have been some difficulties in explaining the exact phenomenology of this seizure, even when talking with neurologists. The apparent paradox is how to understand normal and purposeful behaviour during a temporal lobe seizure. They seemed to be mutually exclusive. The pathophysiology of the TEA, however, can be understood as seizure ('electrographic') restricted only to bilateral hippocampal structures[2]. As a consequence the clinical result will be a complete inability to incorporate facts and events

that occurred during the seizure into the long-term memory. As the abnormal activity remains restricted to both hippocampus and does not involve neocortical temporal areas, there is no change in behaviour. Indeed, Palmini *et al.* surmised and proved, with an intracranial stimulation and recording, that TEA can be caused by bilateral hippocampal spread of abnormal activity[2]. The pathway necessary for contralateral spread of abnormal activity was postulated to be the posterior hippocampal comissure, confirmed to be existent in humans by Gloor *et al.* posteriorly[20].

Once this seizure starts, we would predict continuous hippocampal epileptic discharges. As a consequence of this electrical instability, patients are not able to incorporate their on-going perceptions and events into long-term memory. A similar mechanism was proposed by Manes *et al.*[21]. This can explain the deficits in their autobiographical memory as demonstrated by Zeman *et al.*[17]. In addition, as pointed out by Bergin *et al.*[22], autobiographical memory can be encoded by both verbal (left hippocampus) and non-verbal (visual; right hippocampus) representations, so that autobiographical amnesia implies bilateral hippocampal dysfunction[2, 3, 17, 21–24]. In fact they demonstrated that patients with MTLE epilepsy have impaired remote memory dysfunction compared with patients with extratemporal and generalized epilepsies[22].

Future work should provide epidemiological data to establish the prevalence of TEA among different age groups, if it exists at all, and whether they are seen more frequently with other types of seizures or a sole manifestation of epilepsy.

Some questions that need to be addressed are: Can it be considered a peculiar age- related epileptic syndrome, characterized by subtle frequent seizures and an impaired remote memory function[17]? Is TEA more prevalent in patients with very mild Alzheimer disease[25] or with age-related memory impairment? In addition, as the indication of surgery is based on an analysis of various indicators of a favorable surgical outcome, the presence of TEA can be analyzed as another variable indicating post-operative memory dysfunction.

I propose that TEA is an entity which requires further investigation. Clearly, future studies will be hampered by the problems of diagnosis highlighted above. Assessing for a seizure type which the patient has no memory of, and during which they behave appropriately, is far from easy. However, in the first instance, prospective studies targeting likely high-risk groups would seem appropriate. Patients with presumed early onset dementia, patients with age-related memory impairment and older patients with long-standing temporal lobe epilepsy are potential target groups. If patients with PAS can be identified, measurement of MRI parameters, such as hippocampal volumes and neuropsychological studies, may provide information that is pertinent both to the clinical and surgical[14, 23, 24] management of this seizure type and also to the mechanism underlying memory function.

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